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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/735,910	12/16/2003	Ru Chih C. Huang	2240-199065	3871

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EXAMINER	
ROYDS, LESLIE A	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/735,910	HUANG ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,10,15,18-20 and 22-33* is/are pending in the application.

4a) Of the above claim(s) *22-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,10,15,18-20,32 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *16 December 2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 9-10, 15, 18-20 and 22-33 are presented for examination.

Applicant's Amendment filed May 17, 2007 has been received and entered into the present application. Accordingly, the specification at page 1 is amended.

Claims 9-10, 15, 18-20 and 22-33 are pending. Claims 9-10, 15, 18-20 and 32-33 remain under examination and claims 22-31 remain withdrawn from consideration pursuant to 37 C.F.R. 1.142(b). Claims 9-10, 18 and 32-33 are amended and claims 11-14 and 16 are cancelled.

Applicant's amendments and arguments, filed May 17, 2007, have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Information Disclosure Statement of December 16, 2003

Applicant's submission of the missing references designated as Cite Nos. 17-19 and 21-24 on the Information Disclosure Statement (IDS) of December 16, 2003 in the reply filed May 17, 2007 have each been received and entered into the present application. As reflected by the attached copy of form PTO/SB/08A (two pages total), the Examiner has considered the cited references.

Claim Rejections - 35 USC § 102 (New Grounds of Rejection)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 9-10, 15 and 18-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Howell et al. (U.S. Patent No. 5,541,232; 1996).

Howell et al. teaches a method for the inhibition and/or reversal of multidrug resistant phenomenon in a patient and thereby treatment of both solid malignant tumors and hematological malignancies comprising the administration of NDGA (*meso*-1,4-bis(3,4-dihydroxyphenyl-2,3-dimethylbutane; col.4, l.33-34) or an analogue thereof (abstract and col.5, l.22-41), such as, e.g., the meso isomer of 1,4-bis(3,4-dimethoxy-phenyl)-2,3-dimethylbutane (col.6, l.3-7 and col.16, l.18-col.17, l.9), to said patient, wherein the hematologic malignancy is, e.g., childhood leukemia, acute or chronic leukemia (col.6, l.35-40 and col.16, l.18-col.17, l.9), and further wherein the catecholic butane may be formulated in combination with a pharmaceutically acceptable additives or adjuvants (col.15, l.49-59), such as, e.g., penetration enhancers, such as dimethylsulfoxide (col.7, l.3-15), and may be applied topically, orally or parenterally to the treatment site (col.6, l.52-53). Howell et al. discloses the treatment of mammals, including humans (col.6, l.39-40).

The elected compound tetra-O-methylnordihydroguaiaretic acid is also known as the meso isomer of 1,4-bis(3,4-dimethoxyphenyl)-(2R,3S)-dimethylbutane (please see Figure 1 of the instant drawings), which corresponds directly to the chemical compound of Howell et al. Please also reference Howell et al. at col.6, l.3-17, where the reference further discloses all stereoisomeric configurations of the disclosed compound 1,4-bis(3,4-dimethoxyphenyl)-dimethylbutane, which anticipates the presently claimed limitation of the (2R,3S) configuration of the elected species.

Claim Rejections - 35 USC § 103 (New Grounds of Rejection)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 9-10, 15, 18-20 and 32-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Howell et al. (U.S. Patent No. 5,541,232; 1996).

Howell et al. teaches a method for the inhibition and/or reversal of multidrug resistant phenomenon in a patient and thereby treatment of both solid malignant tumors and hematological malignancies comprising the administration of NDGA (*meso*-1,4-bis(3,4-dihydroxyphenyl-2,3-dimethylbutane; col.4, l.33-34) or an analogue thereof (abstract and col.5, l.22-41), such as, e.g., the meso isomer of 1,4-bis(3,4-dimethoxy-phenyl)-2,3-dimethylbutane (col.6, l.3-7 and col.16, l.18-col.17, l.9), to said patient, wherein the hematologic malignancy is, e.g., childhood leukemia, acute or chronic leukemia (col.6, l.35-40 and col.16, l.18-col.17, l.9), and further wherein the catecholic butane may be formulated in combination with a pharmaceutically acceptable additives or adjuvants (col.15, l.49-59), such as, e.g., penetration enhancers, such as dimethylsulfoxide (col.7, l.3-15), and may be applied topically, orally or parenterally to the treatment site (col.6, l.52-53). Howell et al. discloses the treatment of mammals, including humans (col.6, l.39-40).

As previously stated *supra*, the elected compound tetra-O-methylnordihydroguaiaretic acid is also known as the meso isomer of 1,4-bis(3,4-dimethoxyphenyl)-(2R,3S)-dimethylbutane (please see Figure 1 of the instant drawings), which corresponds directly to the chemical compound of Howell et al.. Please

also reference Howell et al. at col.6, l.3-17, where the reference further discloses all stereoisomeric configurations of the disclosed compound 1,4-bis(3,4-dimethoxyphenyl)-dimethylbutane, which clearly teaches the presently claimed limitation of the (2R,3S) configuration of the elected species.

The differences between the Howell et al. reference and the presently claimed subject matter lies in that the reference fails to teach the particular concentrations of tetra-O-methylnordihydroguaiaretic acid as recited in present claims 32-33.

However, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because Howell et al. expressly recognizes the need to vary the effective dosage amount depending upon the condition to be treated and the analog used. Howell et al. states, "The amount of catecholic butane which should be administered will depend, among other factors, on the purpose for which it is being used. When the catecholic compound is being administered to prevent or treat multidrug resistance, then an amount sufficient to achieve such prevention or treatment should be administered. In a composition comprising a catecholic butane and an antineoplastic agent, then a sufficient amount of the catecholic butane would preferably be included that will improve the effectiveness or the therapeutic index of the antineoplastic agent. Other amounts can readily be determined by one skilled in the art." (col.8, l.30-40)

It is obvious from the above teachings that Howell et al. expressly contemplates variation in the dosage amounts of the active catecholic butane compound and specifically acknowledges that such a matter was well within the skill of the artisan at the time of the invention and would not have required undue experimentation or have been outside the realm of knowledge generally available to the skilled artisan. Factors that would have been taken into consideration when making such a determination would have included, but not have been limited to, the age, weight, sex, diet and medical condition of the patient, severity of the disease, the route of administration, pharmacological considerations, such as the

activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the concentrations that would have actually been employed would have varied widely and, in the absence of evidence to the contrary, the currently claimed specific concentrations are not seen to be inconsistent with that which is presently claimed.

In addition, the concentration of the active ingredient is a result-effective variable, i.e., a variable that achieves a recognized result, and, therefore, the determination of the optimum workable dosage range would be well within the practice of routine experimentation by the skilled artisan, absent factual evidence to the contrary, and, further, absent any evidence demonstrating a patentable difference between the compositions used and the criticality of the amount(s).

Double Patenting (New Grounds of Rejection)

Obviousness-Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Provisional Rejections

Claims 9-10, 15, 18-20 and 32-33 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 21, 24-26, 30-32, 35, 39-50, 54-62 and 64-72 of U.S. Patent Application No. 11/284,111.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s).

Although the conflicting claims are not identical, the claims of the instant patent application and those of the cited copending application are not considered patentably distinct from each other because the pending claims are rendered obvious by the copending claims.

The copending claims clearly provide for the treatment of leukemia by administering a catecholic butane compound, such as, e.g., tetra-O-methylnordihydroguaiaretic acid (i.e., the elected compound), in combination with a pharmaceutically acceptable carrier or excipient, such as, e.g., dimethylsulfoxide. Though the instant claims further define the subject to be treated as a mammal or, more specifically, a human, where the copending claims merely recite a "subject", the administration and adaptation of the therapeutic method of the copending claims to a mammalian subject, including a human, would have naturally commended itself, and would have been *prima facie* obvious, to one of ordinary skill in the art at the time of the invention motivated by a desire to treat mammals and humans suffering from hematologic malignancies, such as leukemia, for which a minimal number of effective therapies are known.

Furthermore, though the copending claims and the instant claims differ with respect to the desired dosage amount(s) for administration, the determination of the optimum concentration of tetra-O-methylnordihydroguaiaretic acid to be used to treat the leukemia would have been well within the routine skill of the artisan and would have taken into account the age, weight, sex, diet and medical condition of the patient, severity of the disease, the route of administration, pharmacological considerations, such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug

combination. Thus, the concentrations that would have actually been employed in the copending claims would have varied widely and, in the absence of evidence to the contrary, are not seen to be significantly inconsistent with those of the present claims.

Accordingly, provisional rejection of claims 9-10, 15, 18-20 and 32-33 is proper over claims 21, 24-26, 30-32, 35, 39-50, 54-62 and 64-72 of copending U.S. Patent Application No. 11/284,111 as claiming obvious and unpatentable variants thereof.

Conclusion

Rejection of claims 9-10, 15, 18-20 and 32-33 remains proper and is **maintained**.

Claims 22-31 remain **withdrawn** from consideration pursuant to 37 C.F.R. 1.142(b).

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Leslie A. Royds
Patent Examiner
Art Unit 1614

August 12, 2007

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER

8/16/07